

Amendments to The Claims

The following listing of claims replaces all prior versions and listings of the claims in this application.

Listing of the Claims

1. (Currently Amended) A method of treating myocardial ischemia ~~and angina~~ in a patient in need thereof comprising administration of a controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem including the pharmaceutically acceptable salts thereof, for evening dosing every 24 hours containing from about 180 mg to about 420 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a C_{max} of Diltiazem in the blood at between about 10 hours and about 17 hours (T_{max}) after administration of the preparation, the preparation being in a sustained-release dosage form in which the form of Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the form of Diltiazem
 - (i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:
 - (a) between about 1% and about 15% after 2 hours;
 - (b) between about 7% and about 35% after 4 hours;
 - (c) between about 30% and about 58% after 8 hours;
 - (d) between about 55% and about 80% after 14 hours; and
 - (e) and in excess of about 75% after 24 hours;

and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of the buffered medium:

- (a) between about 1% and about 25% after about 2 hours;
- (b) between about 7% and about 45% after about 4 hours;
- (c) between about 30% and about 68% after about 8 hours;
- (d) in excess of about 75% after about 24 hours.

2. (Currently Amended) A method of treating myocardial ischemia ~~and-angina~~ in a patient in need thereof comprising administration of a controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem including the pharmaceutically acceptable salts thereof, for evening dosing every 24 hours containing from about 180 mg to about 420 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a C_{max} of Diltiazem in the blood at between about 10 hours and about 17 hours (T_{max}) after administration, the preparation being in a sustained-release dosage form in which the form of Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the form of Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

- (a) between about 4% and about 8% after 2 hours;
- (b) between about 16% and about 21% after 4 hours;
- (c) between about 44% and about 52% after 8 hours;
- (d) between about 69% and about 76% after 14 hours; and
- (e) in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH of about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of the buffered medium:

- (a) between about 4% and about 15% after about 2 hours;
 - (b) between about 16% and about 30% after about 4 hours;
 - (c) between about 44% and about 62% after about 8 hours;
 - (d) in excess of about 80% after 24 hours.
3. (Original) The method of claim 1 wherein the C_{\max} of Diltiazem in the blood is obtained between about 11- about 13 hours after administration of the preparation.
4. (Original) The method of claim 2 wherein the C_{\max} of Diltiazem in the blood is obtained between about 11- about 13 hours after administration of the preparation.
5. (Previously Presented) The method of claim 1, or 2, wherein the preparation is a diffusion controlled preparation.
6. (Previously Presented) The method of claim 1, or 2, wherein the preparation releases the form of Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution.
7. (Cancelled)
8. (Cancelled)
9. (Previously Presented) The method of claim 1, or 2, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises the form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent.
10. (Previously Presented) The method of claim 1, or 2, wherein the preparation comprises a plurality of microgranules each microgranule comprising a central core containing the form of

Diltiazem coated with a microporous membrane and the central core comprises the form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the form of Diltiazem is mixed with the wetting agent.

11. (Previously Presented) The method of claim 1, or 2, wherein the preparation comprises a plurality of microgranules each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and the central core comprises the form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the form of Diltiazem is mixed with the wetting agent wherein the wetting agent assists to maintain the solubility of the form of Diltiazem in each bead, ensuring that the solubility of the form of Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein.
12. (Previously Presented) The method of claim 1, or 2, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and the central core comprises the form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.
13. (Previously Presented) The method of claim 1, or 2, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and the central core comprises the form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent wherein the preparation comprises a mixture of the form of Diltiazem and/or pharmaceutically acceptable salt with the wetting agent and the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.

14. (Previously Presented) The method of claim 1, or 2, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and the central core comprises the form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent wherein the membrane comprises a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester and hydroxypropylmethylcellulose.
15. (Previously Presented) The method of claim 1, or 2, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and the central core comprises the form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the form of diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside).
16. (Previously Presented) The method of claim 9 wherein the form of Diltiazem is mixed with the wetting agent and the membrane comprises N,N,N-trimethyl-2-[(2-methyl-1-oxo-2-propenyl)oxy]-chloride ethanaminium polymer with ethyl-2-propenoate and methyl-2-methyl-2-propenoate, an acrylic polymer and plasticizer combined to form the membrane thereby providing a mechanism of release from this membrane which "washes" the form of diltiazem through pores created when the plasticizer incorporated in the membrane, is released in gastrointestinal fluid.
17. (Previously Presented) The method of claim 1, or 2, wherein the preparation comprises a plurality of microgranules comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises the form of Diltiazem or a pharmaceutically acceptable salt thereof associated with a dissolution agent (other than a wetting agent) to assist in the release of the form of Diltiazem from the preparation.
18. (Previously Presented) The method of claim 1, or 2, wherein the preparation comprises a plurality of microgranules comprising a central core containing the form of diltiazem coated with

a microporous membrane and the central core comprises Diltiazem or a pharmaceutically acceptable salt thereof associated with a dissolution agent (other than a wetting agent) to assist in the release of the form of Diltiazem from the preparation and wherein the dissolution agent is an organic acid selected from the group consisting of adipic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid, tartaric acid which permits the form of diltiazem to dissolve in gastrointestinal fluids when the microgranules pass into the higher pH regions of the gastrointestinal tract of the intestine at which pH diltiazem is much less soluble.

19. (Currently Amended) A method of treating myocardial ischemia ~~and-angina~~ in a patient in need thereof comprising the administration of said preparation of claim 1 to the patient in the evening for effective treatment of the patient's myocardial ischemia ~~and-angina~~ the next morning.
20. (Currently Amended) A method of treating myocardial ischemia ~~and-angina~~ in a patient in need thereof comprising the administration of the preparation of claim 2 to the patient in the evening for effective treatment of the myocardial ischemia ~~and-angina~~ the next morning.
21. (Currently Amended) A method of treating myocardial ischemia ~~and-angina~~ in a patient in need thereof comprising the administration of the preparation of claim 3 to the patient in the evening for effective treatment of the patient's myocardial ischemia ~~and-angina~~ the next morning.
22. (Currently Amended) A method of treating myocardial ischemia ~~and-angina~~ in a patient in need thereof comprising the administration of the preparation of claim 4 to the patient in the evening for effective treatment of the patient's myocardial ischemia ~~and-angina~~ the next morning.
23. (Currently Amended) A method of treating myocardial ischemia ~~and-angina~~ in a patient in need thereof comprising the administration of the preparation of claim 5 to the patient in the evening for effective treatment of the patient's myocardial ischemia ~~and-angina~~ the next morning.
24. (Currently Amended) A method of treating myocardial ischemia ~~and-angina~~ in a patient in need thereof comprising the administration of the preparation of claim 6 to the patient in the evening for effective treatment of the patient's myocardial ischemia ~~and-angina~~ the next morning.
25. (Cancelled)

26. (Cancelled)

27. (Currently Amended) A method of treating myocardial ischemia ~~and angina~~ in a patient in need thereof comprising the administration of the preparation of claim 9 to the patient in the evening for effective treatment of the patient's myocardial ischemia ~~and angina~~ the next morning.

28. (Currently Amended) A method of treating myocardial ischemia ~~and angina~~ in a patient in need thereof comprising the administration of the preparation of claim 10 to the patient in the evening for effective treatment of the patient's myocardial ischemia ~~and angina~~ the next morning.

29. (Currently Amended) A method of treating myocardial ischemia ~~and angina~~ in a patient in need thereof comprising the administration of the preparation of claim 11 to the patient in the evening for effective treatment of the patient's myocardial ischemia ~~and angina~~ the next morning.

30. (Currently Amended) A method of treating myocardial ischemia ~~and angina~~ in a patient in need thereof comprising the administration of the preparation of claim 12 to the patient in the evening for effective treatment of the patient's myocardial ischemia ~~and angina~~ the next morning.

31. (Currently Amended) A method of treating myocardial ischemia ~~and angina~~ in a patient in need thereof comprising the administration of the preparation of claim 13 to the patient in the evening for effective treatment of the patient's myocardial ischemia ~~and angina~~ the next morning.

32. (Currently Amended) A method of treating myocardial ischemia ~~and angina~~ in a patient in need thereof comprising the administration of the preparation of claim 14 to the patient in the evening for the effective treatment of the patient's myocardial ischemia ~~and angina~~ the next morning.

33. (Currently Amended) A method of treating myocardial ischemia ~~and angina~~ in a patient in need thereof comprising the administration of the preparation of claim 15 to the patient in the evening for effective treatment of the patient's myocardial ischemia ~~and angina~~ the next morning.

34. (Currently Amended) A method of treating myocardial ischemia ~~and angina~~ in a patient in need thereof comprising the administration of the preparation of claim 16 to the patient in the evening for effective treatment of the myocardial ischemia ~~and angina~~ the next morning.

35. (Currently Amended) A method of treating myocardial ischemia ~~and-angina~~ in a patient in need thereof comprising the administration of the preparation of claim 17 to the patient in the evening for effective treatment of the myocardial ischemia ~~and-angina~~ the next morning.
36. (Currently Amended) A method of treating myocardial ischemia ~~and-angina~~ in a patient in need thereof comprising the administration of the preparation of claim 18 to the patient in the evening for effective treatment of the myocardial ischemia ~~and-angina~~ the next morning.
37. (Currently Amended) A method of treating myocardial ischemia ~~and-angina~~ in a patient in need thereof comprising the administration of the preparation of claim 1 to the patient in the evening for effective treatment of the patient's myocardial ischemia ~~and-angina~~ over a twenty-four hour period.
38. (Currently Amended) A method of treating myocardial ischemia ~~and-angina~~ in a patient in need thereof comprising the administration of the preparation of claim 2 to the patient in the evening for effective treatment of the myocardial ischemia ~~and-angina~~ over a twenty-four hour period.
39. (Currently Amended) A method of treating myocardial ischemia ~~and-angina~~ in a patient in need thereof comprising the administration of the preparation of claim 3 to the patient in the evening for effective treatment of the patient's myocardial ischemia ~~and-angina~~ over a twenty-four hour period.
40. (Currently Amended) A method of treating myocardial ischemia ~~and-angina~~ in a patient in need thereof comprising the administration of the preparation of claim 4 to the patient in the evening for effective treatment of the patient's myocardial ischemia ~~and-angina~~ over a twenty-four hour period.
41. (Currently Amended) A method of treating myocardial ischemia ~~and-angina~~ in a patient in need thereof comprising the administration of the preparation of claim 5 to the patient in the evening for effective treatment of the patient's myocardial ischemia ~~and-angina~~ over a twenty-four hour period.

42. (Currently Amended) A method of treating myocardial ischemia ~~and angina~~ in a patient in need thereof comprising the administration of the preparation of claim 6 to the patient in the evening for effective treatment of the patient's myocardial ischemia ~~and angina~~ over a twenty-four hour period.
43. (Cancelled)
44. (Cancelled)
45. (Currently Amended) A method of treating myocardial ischemia ~~and angina~~ in a patient in need thereof comprising the administration of the preparation of claim 9 to the patient in the evening for effective treatment of the patient's myocardial ischemia ~~and angina~~ over a twenty-four hour period.
46. (Currently Amended) A method of treating myocardial ischemia ~~and angina~~ in a patient in need thereof comprising the administration of the preparation of claim 10 to the patient in the evening for effective treatment of the patient's myocardial ischemia ~~and angina~~ over a twenty-four hour period.
47. (Currently Amended) A method of treating myocardial ischemia ~~and angina~~ in a patient in need thereof comprising the administration of the preparation of claim 11 to the patient in the evening for effective treatment of the patient's myocardial ischemia ~~and angina~~ over a twenty-four hour period.
48. (Currently Amended) A method of treating myocardial ischemia ~~and angina~~ in a patient in need thereof comprising the administration of the preparation of claim 12 to the patient in the evening for effective treatment of the patient's myocardial ischemia ~~and angina~~ over a twenty-four hour period.
49. (Currently Amended) A method of treating myocardial ischemia ~~and angina~~ in a patient in need thereof comprising the administration of the preparation of claim 13 to the patient in the evening for effective treatment of the patient's myocardial ischemia ~~and angina~~ over a twenty-four hour period.

50. (Currently Amended) A method of treating myocardial ischemia ~~and-angina~~ in a patient in need thereof comprising the administration of the preparation of claim 14 to the patient in the evening for the effective treatment of the patient's myocardial ischemia ~~and-angina~~ over a twenty-four hour period.

51. (Currently Amended) A method of treating myocardial ischemia ~~and-angina~~ in a patient in need thereof comprising the administration of the preparation of claim 15 to the patient in the evening for effective treatment of the patient's myocardial ischemia ~~and-angina~~ over a twenty-four hour period.

52. (Currently Amended) A method of treating myocardial ischemia ~~and-angina~~ in a patient in need thereof comprising the administration of the preparation of claim 16 to the patient in the evening for effective treatment of the myocardial ischemia ~~and-angina~~ over a twenty-four hour period.

53. (Currently Amended) A method of treating myocardial ischemia ~~and-angina~~ in a patient in need thereof comprising the administration of the preparation of claim 17 to the patient in the evening for effective treatment of the myocardial ischemia ~~and-angina~~ over a twenty-four hour period.

54. (Currently Amended) A method of treating myocardial ischemia ~~and-angina~~ in a patient in need thereof comprising the administration of the preparation of claim 18 to the patient in the evening for effective treatment of the myocardial ischemia ~~and-angina~~ over a twenty-four hour period.

55. (Previously Presented) The method of claim 1, or 2, wherein the preparation contains 180 mg of Diltiazem.

56. (Previously Presented) The method of claim 1, or 2, wherein the preparation contains 360 mg of Diltiazem.

57. (Previously Presented) The method of claim 1, or 2, wherein the preparation contains 420 mg of Diltiazem.

58. (Currently Amended) A method of treating myocardial ischemia ~~and angina~~ in a patient in need thereof comprising administration of a controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem including the pharmaceutically acceptable salts thereof, for evening dosing every 24 hours containing from about 180 mg to about 420 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation, for providing a C_{max} of Diltiazem in the blood at between about 10 hours and about 17 hours (T_{max}) after administration of the preparation, the preparation being in a sustained-release dosage form in which the form of Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

- (a) between about 1% and about 15% after 2 hours;
- (b) between about 7% and about 35% after 4 hours;
- (c) between about 30% and about 58% after 8 hours;
- (d) between about 55% and about 80% after 14 hours; and
- (e) and in excess of about 75% after 24 hours; ;

and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of the buffered medium:

- (a) between about 1% and about 25% after about 2 hours;
- (b) between about 7% and about 45% after about 4 hours;
- (c) between about 30% and about 68% after about 8 hours;

(d) in excess of about 75% after about 24 hours wherein the preparation comprises a plurality of microgranules, wherein each microgranule comprises a central core of the form of diltiazem or a pharmaceutically acceptable salt thereof, associated with a wetting agent, wherein the central core is coated with a microporous membrane and wherein the wetting agent is selected from the group consisting of:

sugars;

saccharose, mannitol, sorbitol;

lecithins;

C₁₂ to C₂₀ fatty acid esters of saccharose;

xylose esters or xylites;

polyoxyethylenic glycerides;

esters of fatty acids and polyoxyethylene;

sorbitan fatty acid esters;

polyglycides-glycerides and polyglycides-alcohols esters and

Metal salts.

59. (Original) The method of claim 9 wherein the wetting agent is in association with the diltiazem in the microgranule and not mixed therewith, the membrane comprises a water-soluble or water dispersible polymer or copolymer and a water-, acid- and base-insoluble polymer which is a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester enabling the bead to be hydrated by the introduction of intestinal fluids into the core hydrating the core and therefore mixing the diltiazem and the wetting agent.

60. (Currently Amended) A method of treating myocardial ischemia ~~and angina~~ in a patient in need thereof comprising the administration of the preparation of claim 58 to the patient in the evening for effective treatment of the patient's myocardial ischemia ~~and angina~~ the next morning.

61. (Currently Amended) A method of treating myocardial ischemia ~~and-angina~~ in a patient in need thereof comprising the administration of the preparation of claim 3 to the patient in the evening for effective treatment of the patient's myocardial ischemia ~~and-angina~~ the next morning wherein each microgranule comprises a central core of the form of diltiazem or a pharmaceutically acceptable salt thereof, associated with a wetting agent, wherein the central core is coated with a microporous membrane and wherein the wetting agent is in association with the diltiazem in the microgranule and not mixed therewith, the membrane comprises a water-soluble or water dispersible polymer or copolymer and a water-, acid- and base-insoluble polymer which is a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester enabling the bead to be hydrated by the introduction of intestinal fluids into the core hydrating the core and therefore mixing the diltiazem and the wetting agent.

62. (Currently Amended) A method of treating myocardial ischemia ~~and-angina~~ in a patient in need thereof comprising the administration of the preparation of claim 3 to the patient in the evening for effective treatment of the patient's myocardial ischemia ~~and-angina~~ over a twenty-four hour period wherein each microgranule comprises a central core of the form of diltiazem or a pharmaceutically acceptable salt thereof, associated with a wetting agent, wherein the central core is coated with a microporous membrane and wherein the wetting agent is in association with the diltiazem in the microgranule and not mixed therewith, the membrane comprises a water-soluble or water dispersible polymer or copolymer and a water-, acid- and base-insoluble polymer which is a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester enabling the bead to be hydrated by the introduction of intestinal fluids into the core hydrating the core and therefore mixing the diltiazem and the wetting agent.

63. (Currently Amended) A method of treating myocardial ischemia ~~and-angina~~ in a patient in need thereof comprising administration of a controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem including the pharmaceutically acceptable salts thereof, for evening dosing every 24 hours containing from about 180 mg to about 420 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a C_{max} of Diltiazem in the blood at between about 10 hours and about 17 hours (T_{max}) after administration of the preparation, the preparation being

in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

- (a) between about 1% and about 15% after 2 hours;
- (b) between about 7% and about 35% after 4 hours;
- (c) between about 30% and about 58% after 8 hours;
- (d) between about 55% and about 80% after 14 hours; and
- (e) and in excess of about 75% after 24 hours;

and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of the buffered medium:

- (a) between about 1% and about 25% after about 2 hours;
- (b) between about 7% and about 45% after about 4 hours;
- (c) between about 30% and about 68% after about 8 hours;
- (d) in excess of about 75% after about 24 hours, wherein the preparation comprises a plurality of microgranules, wherein each microgranule comprises a central core of the form of diltiazem or a pharmaceutically acceptable salt thereof, associated with a wetting agent, wherein the central core is coated with a microporous membrane in which the core and membrane comprise:

% W/W

| | | |
|-----|-------------------------|-------|
| (a) | Diltiazem hydrochloride | 69-73 |
|-----|-------------------------|-------|

| | | |
|-----|--|----------------------|
| (b) | Microcrystalline cellulose | 8-9.5 |
| (c) | Povidone K30 | 1-2 |
| (d) | Sucrose stearate | 7-8 |
| (e) | Magnesium stearate NF | 0.5-2.5 |
| (f) | Talc USP | 0.5-5.0 |
| (g) | Titanium dioxide (USP) | 0.15-0.3 |
| (h) | Hydroxypropylmethylcellulose 2910 | 0.3-0.6 |
| (i) | Polysorbate 80 (tween) | 0.01-0.025 |
| (j) | Simeticone C emulsion USP (dry of 30%) | 0.01-0.015 |
| (k) | a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry 30%) | 7-11 |
| | Purified water USP | 0 (used for mixing). |

64. (Currently Amended) A method of treating myocardial ischemia ~~and angina~~ in a patient in need thereof comprising the administration of the preparation of claim 63 to the patient in the evening for effective treatment of the patient's myocardial ischemia ~~and angina~~ the next morning.

65. (Currently Amended) A method of treating myocardial ischemia ~~and angina~~ in a patient in need thereof comprising the administration of the preparation of claim 63 to the patient in the evening for effective treatment of the patient's myocardial ischemia ~~and angina~~ over a twenty-four hour period.

66. (Currently Amended) A method of treating myocardial ischemia ~~and angina~~ in a patient in need thereof comprising administration of a controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem including the pharmaceutically acceptable salts

thereof, for evening dosing every 24 hours containing about 180 mg to about 420 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a C_{\max} of Diltiazem in the blood at between about 10 hours and about 17 hours (T_{\max}) after administration of the preparation, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

- (a) between about 1% and about 15% after 2 hours;
- (b) between about 7% and about 35% after 4 hours;
- (c) between about 30% and about 58% after 8 hours;
- (d) between about 55% and about 80% after 14 hours; and
- (e) and in excess of about 75% after 24 hours; ;

and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of the buffered medium:

- (a) between about 1% and about 25% after about 2 hours;
- (b) between about 7% and about 45% after about 4 hours;
- (c) between about 30% and about 68% after about 8 hours;
- (d) in excess of about 75% after about 24 hours, wherein the preparation comprises a plurality of microgranules, wherein each microgranule comprises a central core of the form of diltiazem or a pharmaceutically acceptable salt thereof, associated with a wetting agent, wherein

the central core is coated with a microporous membrane in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with adjuvants.

67. (Currently Amended) A method of treating myocardial ischemia ~~and angina~~ in a patient in need thereof comprising the administration of the preparation of claim 66 to the patient in the evening for effective treatment of the patient's myocardial ischemia ~~and angina~~ the next morning.

68. (Currently Amended) A method of treating myocardial ischemia ~~and angina~~ in a patient in need thereof comprising the administration of the preparation of claim 66 to the patient in the evening for effective treatment of the patient's myocardial ischemia ~~and angina~~ over a twenty-four hour period.

69. (Currently Amended) A method of treating myocardial ischemia ~~and angina~~ in a patient in need thereof comprising administration of a controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem including the pharmaceutically acceptable salts thereof, for evening dosing every 24 hours containing from about 180 mg to about 420 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a C_{max} of Diltiazem in the blood at between about

10 hours and about 17 hours (T_{\max}) after administration of the preparation, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

- (a) between about 1% and about 15% after 2 hours;
- (b) between about 7% and about 35% after 4 hours;
- (c) between about 30% and about 58% after 8 hours;
- (d) between about 55% and about 80% after 14 hours; and
- (e) and in excess of about 75% after 24 hours; ;

and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of the buffered medium:

- (a) between about 1% and about 25% after about 2 hours;
- (b) between about 7% and about 45% after about 4 hours;
- (c) between about 30% and about 68% after about 8 hours;
- (d) in excess of about 75% after about 24 hours, wherein the preparation comprises a plurality of microgranules, wherein each microgranule comprises a central core of the form of diltiazem or a pharmaceutically acceptable salt thereof, associated with a wetting agent, wherein the central core is coated with a microporous membrane in which the core and membrane comprise:

- (i) in the core,

(a) between about 69% and about 73% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

together with adjuvants; and

(ii) in the membrane,

(c) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer; and

(d) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with adjuvants.

70. (Currently Amended) A method of treating myocardial ischemia ~~and angina~~ in a patient in need thereof comprising the administration of the preparation of claim 69 to the patient in the evening for effective treatment of the patient's myocardial ischemia ~~and angina~~ the next morning.

71. (Withdrawn) The method of claim 1, 2 or 58 wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of Diltiazem during the tablet process, together with excipients and adjuvants.

72. (Withdrawn; Currently Amended) A method of treating ~~or preventing~~ myocardial ischemia ~~and angina~~ in a patient in need thereof comprising the administration of the preparation of claim 71 to the patient in the evening for effective treatment ~~or prevention~~ of the patient's myocardial ischemia ~~and angina~~ the next morning.

73. (Withdrawn; Currently Amended) A method of treating ~~or preventing~~ myocardial ischemia ~~and angina~~ in a patient in need thereof comprising the administration of the preparation

of claim 71 to the patient in the evening for effective treatment ~~or prevention~~ of the patient's myocardial ischemia ~~and angina~~ over a twenty-four hour period.

74. (Currently Amended) A method of treating myocardial ischemia ~~and angina~~ in a patient in need thereof comprising administration of a controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem including the pharmaceutically acceptable salts thereof, for evening dosing every 24 hours containing from about 180 mg to about 420 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a C_{\max} of Diltiazem in the blood at between about 10 hours and about 17 hours (T_{\max}) after administration of the preparation, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with adjuvants.

75. (Withdrawn) The method of claim 74 wherein the microgranules are in capsule form.

76. (Withdrawn) The method of claim 74 wherein the microgranules are in tablet form.

77. (Previously Presented) The method of claim 74 wherein the core and membrane comprise:

(i) in the core,

(a) between about 69% and about 73% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 7% and about 8% wetting agent (% w/w of the total preparation); together with adjuvants; and

(ii) in the membrane,

(c) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer; and

(d) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with adjuvants.

78. (Currently Amended) A method of treating myocardial ischemia ~~and angina~~ in a patient in need thereof comprising administration of a controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem including the pharmaceutically acceptable salts thereof, for evening dosing every 24 hours containing from about 180 mg to about 420 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a C_{max} of Diltiazem in the blood at between about 10 hours and about 17 hours (T_{max}) after administration of the preparation, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or

pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with adjuvants wherein the core and membrane comprise:

| | % W/W |
|--|----------|
| (a) Diltiazem hydrochloride | 69-73 |
| (b) Microcrystalline cellulose (<u>Avicel ph101</u>) | 8-9.5 |
| (c) Povidone K30 | 1-2 |
| (d) Sucrose stearate (crodesta F150) | 7-8 |
| (e) Magnesium stearate NF | 0.5-2.5 |
| (f) Talc USP | 0.5-5.0 |
| (g) Titanium dioxide (USP) | 0.15-0.3 |

| | | |
|-----|---|----------------------|
| (h) | Hydroxypropylmethylcellulose 2910 | 0.3-0.6 |
| (i) | Polysorbate 80 (tween) | 0.01-0.025 |
| (j) | Simeticone C emulsion USP (dry of 30%) | 0.01-0.015 |
| (k) | a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%) | 7-11 |
| | Purified water USP | 0 (used for mixing). |

79. (Withdrawn) The method of claim 74 wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of Diltiazem during the tablet process, together with excipients and adjuvants.

80. (Currently Amended) A method of treating myocardial ischemia ~~and angina~~ in a patient in need thereof comprising the administration of the preparation of claim 74 to the patient in the evening for effective treatment of the myocardial ischemia the next morning.

81. - 116. (Cancelled)

117. (Currently Amended) The method of claim 1 wherein the method of treating myocardial ischemia ~~and angina~~ in a patient in need thereof reduces the incidences of myocardial ischemia ~~and angina~~ in said patient.